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(54) Title: I_h–MODULATORS

(57) Abstract

The present invention relates to the use of an I_h channel modulator in the manufacture of a medicament for use in psychiatry. To certain novel methanamine derivatives, to processes for their preparation, to pharmaceutical formulations containing them and to their use in medical therapy, particularly for use in psychiatry.

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I_h MODULATORS

The present invention relates to the use of an I_h channel modulator in the manufacture of a medicament for use in psychiatry. To certain novel methanamine derivatives, to processes for their preparation, to pharmaceutical formulations containing them and to their use in medical therapy, particularly for use in psychiatry.

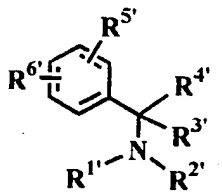
The hyperpolarization activated cation current (I_h), also indicated as queer or anomolous rectifier current (I_q and I_{AR} respectively), is a membrane current that is carried by I_h channels, with the characteristics that it activates at potentials around or below resting membrane potential. It is carried by both sodium and potassium ions and is unique in that it does not pass lithium ions. The current reverses at approximately -30 mV and the time constant of activation varies with membrane potential, temperature, intracellular cAMP concentration, and other modulators, but typically is about 200 ms at -120 mV at room temperature. I_h is blocked by 1-5 mM caesium (Cs^+) (Pape H.C. (1996) Annu.Rev.Physiol. 58:299-327). The I_h channel is not blocked by 1mM barium (Ba^{2+}).

Pape H.C. (Neuroscience 1994 59(2), 363-73) showed that zatebradine (UL-FS49) and its derivative DK-AH268, known as a specific bradycardic agents, are capable of reducing the conductance underlying I_h at concentrations in the range of 1E-5 to 1E-3 M. Apparently the mechanism involved is a use-dependent blockade with no alteration in the gating properties. ZD7288 (4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino)-pyrimidinium-chloride), which also has selective bradycardic properties, was shown to be capable of blocking I_h with an IC_{50} of 2E-6 M (Harris, N.C. and Constanti, A., 1995, J. Neurophysiol., 74(6): 2366-2378). ZD7288 is thought to be a selective blocker of Ih since it did not significantly affect other bioelectrical cell properties. Similar data have been published previously (Harris, N.C., Libri, V. and Constanti, A., 1994, Neurosci. Lett., 176: 221-225) for ZM227189, a triazinium iodide derivative of ZD7288.

It has now surprisingly been found that I_h channel modulators are effective in the treatment or prevention of psychiatric disorders, including depression, anxiety and psychosis.

Accordingly, the present invention provides the use of an I_h channel modulator in the manufacture of a medicament for the treatment or prevention of a psychiatric disorder, including depression, anxiety and psychosis.

The present invention further includes the use of an I_h channel modulator in the manufacture of a medicament for the treatment or prevention of a psychiatric disorder, with the proviso that the modulator is not a compound of formula (D):-

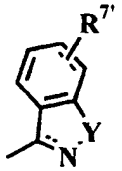

(D)

wherein $R^{1'}$ and $R^{2'}$, which may be the same or different, are each selected from C_{6-12}aryl, C_{2-14}heteroaryl, C_{6-12}arylC_{1-6}alkyl, C_{2-14}heteroarylC_{1-6}alkyl (where the alkyl, aryl or heteroaryl moiety may be optionally substituted by one or more substituents selected from C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{4-6}cycloalkenyl, C_{6-12}aryl, C_{2-14}heteroaryl, halogen, amino, hydroxy, haloC_{1-6}alkyl, nitro, C_{1-6}alkylthio, sulphonamide, C_{1-6}alkylsulphonyl, hydroxy-C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, carboxyl, carboxyC_{1-6}alkyl, carboxamide and C_{1-6}alkylcarboxamide), hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{4-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxyC_{1-6}alkyl (where the alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, or alkoxyalkyl moieties may be optionally substituted by one or more substituents selected from amino, halogen, hydroxy, C_{1-6}alkylcarboxamide, carboxamide, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarboxy and carboxyC_{1-6}alkyl) or one of $R^{1'}$ and $R^{2'}$ are as hereinbefore defined and one is hydroxy;

$R^{3'}$ and $R^{4'}$, which may be the same or different, are each selected from C_{6-12}aryl, C_{2-14}heteroaryl, C_{6-12}arylC_{1-6}alkyl, C_{2-14}heteroarylC_{1-6}alkyl (where the alkyl, aryl or heteroaryl moiety may be optionally substituted by one or more substituents selected from C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{4-6}cycloalkenyl, C_{6-12}aryl, C_{2-14}heteroaryl, halogen, amino, hydroxy, halo-C_{1-6}alkyl, nitro, C_{1-6}alkylthio, sulphonamide, C_{1-6}alkylsulphonyl, hydroxy C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, carboxyl, carboxyC_{1-6}alkyl, C_{1-6}alkylcarboxamide

and carboxamide), hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{4-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{2-6}alkenyl, haloC_{2-6}alkynyl, cyano, carboxyl, C_{1-6}alkylcarboxy and carboxyC_{1-6}alkyl (where the alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, or alkoxyalkyl moieties may be optionally substituted by one or more substituents selected from amino, hydroxy, C_{1-6}alkylcarboxamide, carboxamide, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarboxy and carboxy-C_{1-6}alkyl); or one of $R^{3'}$ or $R^{4'}$ together with one of $R^{1'}$ or $R^{2'}$ and the N atom to which it is attached form a 5- or 6-membered heterocyclic ring.

$R^{5'}$ represents one or more ring substituents selected from halogen, hydrogen C_{1-6}alkyl and C_{1-6}alkoxy; and
$R^{6'}$ represents a single ring substituent of formula:



wherein the dotted line represents an optional bond; Y is oxygen or -$NR^{8'}$ (where $R^{8'}$ is hydrogen or C_{1-6}alkyl) and $R^{7'}$ represents one or more substituents selected from hydrogen, halogen, haloC_{1-6}alkyl, C_{1-6}alkyl and C_{1-6}alkoxy;
or a pharmaceutically acceptable salt or solvate thereof.

The compounds of formula (D) above are disclosed in the international patent application PCT/EP 97/01904 (published as WO 97/40027; AKZO Nobel N.V.). No protection is sought for the compounds of formula (D) per se. Representative compounds according to formula (D) are demonstrated in the present application to corroborate the correlation between Ih channel modulation and psychotropic activity, as measured by inhibition of burying behaviour in mice .

I_h channel modulators can both change I_h channel conductance and/or I_h channel open probability. These terms are well known to a skilled person or described in the literature, for example, Hille, B. *Ionic channels of excitable membranes (second edition)*. Sinauer Associates Inc. Sunderland, Massachusetts, 1992, and *Single-channel recording* (second edition). Sakmann, B. and Neher, E. (eds). Plenum Press, New York, 1995. I_h channel modulators include agents which inhibit the conductance of the channel

and/or the open probability and in particular those modulators which block the I_h channel as assessed by measuring Ih current and/or the change in membrane potential caused by activation or inhibition or block of Ih current. More specifically, I_h channel modulators include modulators with an IC_{50} in the I_h channel functional assay described herein in the range 1E-5 to 1E-12 $mol.l^{-1}$ (pIC_{50} of 5 to 12) or more preferably in the range 1E-6 to 1E-9 $mol.l^{-1}$ (pIC_{50} of 6 to 9).

I_h channel modulators according to the present invention, further include those agents which show at least 5 fold selectivity in potency in the I_h channel functional assay over activity on one or more (including 2, 3 or 4) known ion channel(s), such as voltage-dependent Na^+, K^+ and Ca^{2+} channels as measured in a functional assay (for methods see for example Ogata, N., Yoshii,M., and Narahashi, T., 1989, Brain Res., 476:140-144). More particularly 5 to 10 fold selectivity and preferably 10 fold selectivity or more. I_h channel modulators that show at least 5 fold selectivity in potency in the I_h channel functional assay over activity on one or more (including 2, 3 or 4) known monoaminergic receptor(s), such as the G-protein coupled receptors for noradrenaline, serotonin, dopamine, GABA, glutamate and glycine and ligand-activated ion channels for serotonin, GABA, glutamate and glycine, or the monoaminergic uptake site, such as the membrane transporters for noradrenaline, serotonin, dopamine, GABA, glutamate and glycine, as determined in a functional and/or binding assay known to be specific for that type of receptor or transporter. More particularly 5 to 10 fold selectivity and preferably 10 fold selectivity or more are also included within the scope of the present invention. Included within the scope of the present invention, are I_h channel modulators which have one or more of the aforementioned characteristics.

Depression states in the treatment of which the compounds of formula (I) and their pharmaceutically acceptable salts and solvates are particularly useful, are those classified as affective disorders in the Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition-Revised, American Psychiatric Association, Washington, D.C. (1994), including the mood disorders, other specific affective disorders and bipolar and depressive disorders not otherwise specified.

Other uses in human therapy for the compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof includes the treatment of the following conditions:

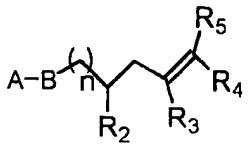
- anxiety disorders, including phobic neuroses, panic neuroses, anxiety neuroses, post-traumatic stress disorder and acute stress disorder.
- attention deficit disorders.
- eating disorders, including obesity, anorexia nervosa and bulimia.
- personality disorders, including borderline personality disorders.
- schizophrenia and other psychotic disorders, including schizo affective disorders, dilusional disorders, shared psychotic disorder, brief psychotic disorder and psychotic disorder.
- narcolepsy-cataplexy syndrome.
- substance related disorders.
- sexual function disorders.

The present invention further provides a method for the treatment or prevention of a psychiatric disorder, including any of the aforementioned disorders or conditions, in an animal, for example, a mammal including a human, which comprises administering to said animal an effective amount of an I_h channel modulator.

A further feature of the present invention includes the use of an I_h channel modulation assay for identifying compounds useful for the treatment or prevention of psychiatric disorders. Such assay can, for example, include taking a brain slice, or a cultured brain slice, or ganglia of the peripheral nervous system, or primary cell cultures of central and/or peripheral nervous tissue, or cell lines expressing Ih channels in order to incubate and/or expose these cells and tissues to test compounds with the aim to assess whether these test compounds affect Ih current and/or the change in membrane potential caused by activation or inhibition or block of Ih current.

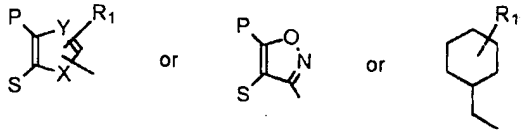
The present invention includes within its scope, compounds which are modulators of the I_h channel, including those novel I_h channel modulators which have the IC_{50} and pIC_{50} values mentioned above and/or the selectivity in the I_h channel functional assay over the activity on one or more (including 2, 3 or 4) known ion channel(s) and/or activity on one or more (including 2, 3 or 4) known monoaminergic receptor(s) or uptake site as mentioned above; with the proviso that the compounds are not the compounds of formula (D) above.

The present invention further includes the compounds (methaneamine derivatives) of formula (I) :



(I)

wherein A is a group selected from (a), (b) or (c):-



(a) (b) (c)

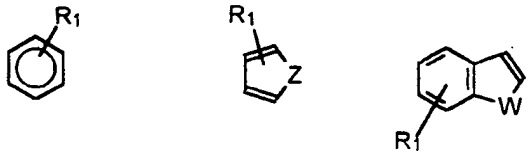
wherein Y is CH or N;

X is O, S, CH=CH, or CH=N;

P and S, which may be the same or different, each represent hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl or pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; or P and S together with the ethylene group to which they are bonded form a 1,2-phenylene, a pyridinediyl (including 2,3- and 3,4-pyridinediyl), or a 1-cyclohexen-1,2-diyl group, which groups may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl;

R_1 represents one or more ring substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl;

B is a bivalent carbon radical derived from an aromatic group selected from (d), (e) or (f):



(d) (e) (f)

wherein Z is O or S; W is O, S or CH=CH; R_1 is as hereinbefore defined;

R_2 is NH_2

R_3, R_4, and R_5, which may be the same or different, each represent halogen, C_{1-4}alkyl or hydrogen, or R_3 and R_4 together form a carbon-carbon bond;

n is 0 or 1;

or a physiologically acceptable salt or solvate thereof;

with the proviso that when A is group (b) wherein P and S together with the ethylene group to which they are bonded form a 1,2-phenylene group, which group may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; R_2, R_3, R_4 and R_5 are as herein before defined and n is 0; then B is a group (e) or (f).

As used herein the term alkyl as a group or part of a group means a straight or branched chain alkyl group. Such alkyl groups include methyl, ethyl, i-propyl, n-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, isopently, neopentyl, n-hexyl, isohexyl and neohexyl. References to alkenyl groups include groups which may be in the E- or Z- form or a mixture thereof and which when they contain at least three carbon atoms, may be branched. Examples of particular alkenyl groups include vinyl, allyl, butenyl, isobutenyl, pentenyl, isopentenyl, hexenyl, isohexenyl, neohexenyl and 1-methyl-2-propenyl. The terms alkoxy and alkynyl have meanings as understood by the person skilled in the art and include straight and branched chains. Examples of alkoxy groups include methoxy and ethoxy and examples of alkynyl groups include ethynyl, propynyl and butynyl.

As used herein the terms cycloalkyl and cycloalkenyl have meanings as understood by the person skilled in the art and include cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl and cyclohexadienyl.

The term halogen includes chloro, bromo, fluoro and iodo. The term halo-C_{1-6}alkyl means an alkyl group in which one or more hydrogens is replaced by halo and preferably containing one, two or three halo atoms. Examples of such groups include trifluoromethyl and fluoroisopropyl.

As used herein the term aryl as a group or part of a group means C_{6-12}aryl aromatic groups and includes one or two C_6 aromatic rings. The term covers fused ring systems as well as systems in which rings are connected through a linking group, for example -N-, -C-, -O- or -S-, or a bond. Examples of such groups include phenyl, naphthyl, and biphenyl.

As used herein the term heteroaryl as a group or part of a group means C_{2-14}heteroaryl aromatic groups optionally substituted with one or more substituents independently selected from hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy and includes one or two C_{5-7} aromatic rings containing one or more (for example, one to three) heteroatoms selected from oxygen, sulphur, and nitrogen. The term includes the substituent R_6 as hereinbefore defined, fused ring systems as well as systems in which rings are connected through a linking group, for example -N-, -C-, -O- or -S-, or a bond. Examples of such groups include 1,2-benzoisoxazolyl, pyridyl, thiadiazolyl, indazolyl, benzofuryl, quinolyl, thienyl and isoquinolyl.

The term 5- and 6- membered heterocyclic ring means a saturated or partially saturated 5- and 6- membered ring. Examples of such saturated groups include piperidinyl and pyrrolidinyl and partially saturated groups include tetrahydropyridinyl.

The term haloC_{1-6}alkyl means an alkyl group in which one or more hydrogens is replaced by halo and preferably containing one, two or three halo atoms. Examples of such groups include trifluorobutyl and trifluoromethyl.

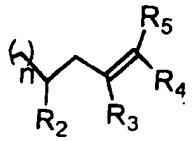
The term haloC_{2-6}alkenyl means an alkenyl group in which one or more hydrogens is replaced by halo and preferably containing one, two or three halo groups. The halo atoms may be present on saturated or unsaturated carbon atoms. Examples of such groups include 2-chloropropenyl, 3,3-difluoropropenyl and 1,1-difluoropropenyl.

The term haloC_{2-6}alkynyl means an alkynyl group in which one or more hydrogens is replaced by halo and preferably containing one, two or three halo groups. The term includes alkynyl groups with a terminal halo atom. Examples of such groups include 3-chloropropynyl and 3-bromopropynyl.

It will be appreciated that some of the compounds of formula (I) and their salts and solvates may contain one or more centres of chirality and exist as stereoisomers including diastereomers and enantiomers. The present invention includes the aforementioned stereoisomers within its scope and each of the individual (R) and (S) enantiomers of the compounds of formula (I) and their salts and solvates substantially free, ie associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer and mixtures of such enantiomers in any proportions including racemic mixtures containing substantially equal amounts of the two enantiomers.

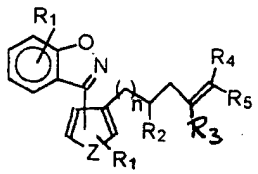
Ring substituent R_1 in formula (I) may be in any one or more of the available ring positions. Specific examples of single ring substituents include 4-chloro, 2 and 4 fluoro or 4-methyl -. Examples of multiple substituents include 2-fluoro-4-methyl, 4-chloro-3-fluoro and 3,4-dichloro.

In formula (I), the A group may be attached to the B group via any available carbon atom and vice versa. The B groups may be attached via any available B group ring carbon atom to the carbon atom of the side chain:



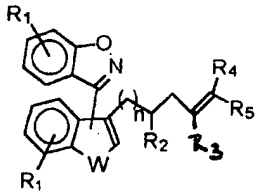
For example, when group A has the structure (a) then the B group may be attached to any of the heterocyclic ring carbons. When group A has the structure (b) then the B group is attached to the A group at position 3 and when the A group has structure (c) then the B group is attached by the methylene carbon. When the B group has structure (d) then the A group may be attached at any position but preferably ortho- related to the side chain. When the B group has structure (e) or (f) then the A group may be attached at positions 2- or 3.

The compounds of formula (I) further include the compounds of formula (IA), (IB) and (IC) below:-



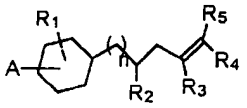
(IA)

wherein Z, R_1, R_2, R_3, R_4 and R_5 are as herein before defined and n is 0; or a physiologically acceptable salt or solvate thereof;



(IB)

wherein W, R_1, R_2, R_3, R_4 and R_5 are as herein before defined and n is 0; or a physiologically acceptable salt or solvate thereof; and



(IC)

wherein A, R_1, R_2, R_3, R_4 and R_5 are as herein before defined and n is 0 or 1, preferably n is 0; or a physiologically acceptable salt or solvate thereof;
with the proviso that A is not a group (b) wherein P and S together with the ethylene group to which they are bonded form a 1,2-phenylene group, which group may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; R_2, R_3, R_4 and R_5 are as herein before defined and n is 0; or a physiologically acceptable salt or solvate thereof.

The compounds of formula (I), (IA), (IB), (IC) and the compounds herein which fall within the scope of formula (I), may hereinafter be referred to as compounds according to the present invention.

Examples of groups of formula A include benzoxazolyl, benzothiazolyl, naphthalenyl, isothiazolyl, thiophenyl, furanyl, isoxazolyl, quinolinyl, isoxazolopyridinyl, 4,5,6,7-tetrahydro-benzisoxozolyl, isoquinolinyl, benzofuranyl, benzothiophenyl, benzisothiazolyl, pyridinyl, phenyl and benzyl. Each of the aforementioned groups may optionally be substituted by a group selected from hydrogen, halogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl. Such subtituted groups include 2-methoxybenzyl, 3-methoxybenzyl, 4-fluorophenyl, 3-cyanophenyl, 3-trifluoromethylphenyl, 3,5-dimethylisoxazol-4-yl, 5-chlorobenzofuran-2-yl and 5-fluorobenzothiophen-2-yl.

Examples of the bivalent carbon radical B are those derived from benzene, furan, benzofuran or thiophene.

Preferred A groups according to the invention include isoxazolopyridinyl, naphthyl, benzofuranyl, benzothiophenyl phenyl, substituted phenyl, tetrahydrobenzisoxazolyl, isoquinolinyl, thiazolyl, furanyl, benzyl.

Preferably radical B is derived from phenyl or thienyl.

Most preferred R_1 groups include hydrogen, fluorine, chlorine, methyl, trifluoromethyl, and methoxy.

Groups R_3, R_4 and R_5 are preferably hydrogen.

For therapeutic use, salts of the compounds of formula (I), (IA), (IB) and (IC) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

Pharmaceutically acceptable acid addition salts include those derived from mineral acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, maleic, malonic, fumaric,

benzoic, ascorbic, propionic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic acids.

Preferred salts according to the invention include hydrochloric, fumaric [(E) butenedioic] and maleic [(Z) butenedioic] acid addition salts.
Solvates according to the invention include hydrates.

In a further aspect of the invention there are provided the compounds of formula (I), (IA), (IB) and (IC) and their pharmaceutically acceptable salts and solvates for use in therapy, more particularly in the treatment or prevention of psychiatric disorders.

The present invention further includes a method for the treatment of an animal, for example, a mammal including a human, suffering from or liable to suffer from a psychiatric disorder or any of the aforementioned disorders or conditions, which comprises administering an effective amount of a compound of formula (I), (IA), (IB) or (IC) or a pharmaceutically acceptable salt or solvate thereof.

In yet a further aspect, the present invention provides the use of a compound of formula (I), (IA), (IB) or (IC) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prevention of a psychiatric disorder or any of the aforementioned disorders or conditions.

The amount of an I_h channel modulator or a compound of formula (I), (IA), (IB) or (IC) or a pharmaceutically acceptable salt or solvate thereof, also referred to herein as the active ingredient, which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated.

A suitable daily dose for any of the above mentioned disorders will be in the range of 0.01 to 100 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 50 mg per kilogram body weight per day and most preferably in the range 0.1 to 10 mg per kilogram body weight per day. The desired dose may be presented as one, two, three, four, five or more sub-doses administered at appropriate intervals throughout th day.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation comprising an I_h channel modulator or a compound of formula (I), (IA), (IB) or (IC) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable carrier thereof and optionally other therapeutic agents. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipients thereof.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal and intravitreal) administration. The formulations may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro *et al.*,Remington's Pharmaceutical Sciences (18th ed., Mack Publishing company, 1990, see especially Part 8 : Pharmaceutical Preparations and their Manufacture). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents and wetting agents.

Formulations suitable for oral administration may be presented as discrete units such as pills, tablets or capsules each containing a predetermined amount of active ingredient; as a powder or granules; as a solution or suspension. The active ingredient may also be presented as a bolus or paste, or may be contained within liposomes.

Formulations for rectal administration may be presented as a suppository or enema.

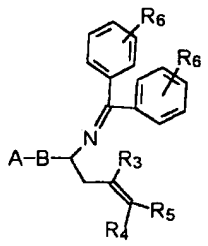
For parenteral administration, suitable formulations include aqueous and non-aqueous sterile injection. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Formulations suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurised aerosols, nebulisers or insufflators.

The present invention further includes the following processes for the preparation of compounds of formula (I), (IA), (IB) and (IC).

According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a physiologically acceptable salt or solvate thereof, which comprises:

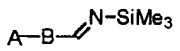
(A) reacting a compound of formula (II)



(II)

wherein R_6 is hydrogen or halogen, with a hydrolysing agent;

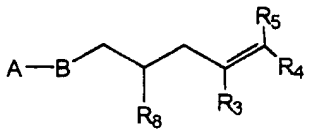
(B) reacting an imine of formula (IIA)



(IIA)

with an appropriate organometallic reagent in the presence of an inert solvent; or

(C) for compounds of formula (I) wherein n is 1, the reduction of a compound of formula (XV)



(XVa)

wherein R_8 is an azido group, and A, B, R_3 R_4 and R_5 are as previously defined; and

where necessary or desired, following processes A to C above, any one or more of the following further steps in any order may be performed:

(i) removing any remaining protecting group(s);

(ii) converting a compound of formula (I) or a protected form thereof into a further compound of formula (I) or a protected form thereof;

(iii) converting a compound of formula (I) or a protected form thereof into a pharmaceutically acceptable salt or solvate of a compound of formula (I) or a protected form thereof;

(iv) converting a pharmaceutically acceptable salt or solvate of a compound of formula (I) or a protected form thereof into a compound of formula (I) or a protected form thereof;

(v) converting a pharmaceutically acceptable salt or solvate of a compound of formula (I) or a protected form thereof into another pharmaceutically acceptable salt or solvate of formula (I);

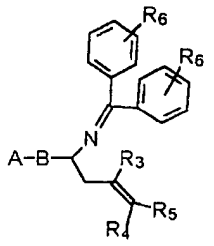
(vi) where the compound of formula (I) is obtained as a mixture of (R) and (S) enantiomers resolving the mixture to obtain the desired enantiomer.

(vii) cleavage of a compound of fomula (I) from a solid phase resin.

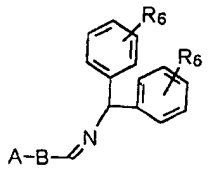
In the following description the symbols A, B, R_1, R_2, R_3, R_4, R_5 and n have the meanings ascribed to them in formula (I) unless otherwise stated.

Process A, may be effected by hydrolysis of compounds of formula (II) wherein R_6 is hydrogen or a halogen, preferably para-fluoro. The reaction can conveniently be carried out in the presence of acid for example 1 M HCl in acetone.

Compounds of formula (II) may be prepared from compounds of formula (III), for example, by deprotonation, typically by addition of base, preferably lithium tert. butoxide in an inert solvent, such as tetrahydrofuran, at a temperature of -100° to 25°C followed by the addition of a reagent $R_4R_5C=C(R_3)CH_2L^1$, in which L^1 is a suitable leaving group, such as mesylate or triflate or, a halo atom including iodo, chloro or bromo. This general process is described by C. Giafranco *et. al.* (J. Org. Chem. 1996, 61, 5134)



(II)



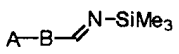
(III)

Compounds of formula (III), wherein R_6 is as hereinbefore described, may be prepared by reacting aldehydes of formula (IV) with an appropriate diaryl-methanamine, such as diphenyl or bis-p-fluorophenylmethanamine. The reaction may be carried out azeotropically by distillation or with a drying agent such as titanium tetrachloride, magnesium sulfate or with molecular sieves in an apolar solvent, for example, methylene chloride.

In an alternative process B compounds of formula (I) may be prepared by reaction of an intermediate imine of formula (IIA), such as that prepared from aldehydes of formula (IV) and lithium bis(trimethylsilyl)amide, with an appropriate organometallic reagent , such as a Grignard, or a lithium or zinc reagent derived from $R_4R_5C=C(R_3)CH_2L^2$ in which L^2 is a suitable leaving group, such as a chloro or bromo atom, in the presence of an inert solvent such as hexane, toluene or tetrahydrofuran, at a temperature of -100°C to 100°C, typically at room temperature. This general process is described by D. J. Hart et. al. (J. Org. Chem. 1983, 48, 289).

A-B-CHO

(IV)



(IIA)

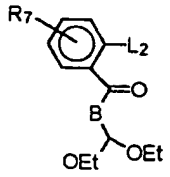
Aldehydes of formula (IV) can be prepared by means of intermolecular palladium coupling reactions using the appropriate trialkyl arylstannyl reagent such as A-$SnBu_3$ with the appropriate bromo or iodo-aryl aldehyde, B(Y)CHO, where Y is a bromo or iodo atom. The reaction may conveniently be carried out in anhydrous xylene solution at 80 - 115 °C using a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0), or by reaction of

an aryl boronic acid reagent, such as A-$B(OH)_2$, with the bromo or iodo-arylaldehydes, in a basic medium, such as 2 N aqueous sodium carbonate solution in a toluene-ethanol mixture at 50-100°C and using the above mentioned catalyst. Alternatively, this coupling may be carried out by reacting the appropriate aryl or heteroaryl derivative A-L^2, where L^2 is a suitable leaving group such as a chloro, bromo or iodo atom; with commercially available 2-formylbenzene boronic acid using the hitherto described reaction conditions.

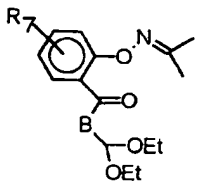
Reagents of formula $R_4R_5C=C(R_3)CH_2L^1$ and $R_4R_5C=C(R_3)CH_2L^2$ may be obtained commercially.

Aldehydes of formula (IV) where A represents a benzisoxazol-3-yl group may be prepared from compounds of formula (VI) where R_7 is hydrogen or halogen and L_2 is a leaving group such as nitro or halogen, preferably fluoro atom via the intermediate compound of formula (V) using the process described by Schutske G. M. (J. Org. Chem., 1984, **49**, 180-183) for the synthesis of 3-phenyl-1,2-benzisoxazole. Hydrolysis to the aldehyde can be carried out using various catalysts, for example dilute acids such as hydrochloric acid at temperatures between 20- 100 °C.

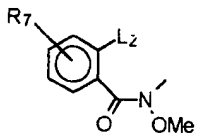
Compounds of formula (VI), in which R_7 represents hydrogen or a halogen atom, in particular fluoro or chloro, may be prepared by the addition of organo- metallic reagents derived from compounds of formula (VII), where L_2 is a suitable leaving group, such as a halo atom including iodo, fluoro, bromo or chloro, using methods well known to a person skilled in the art, to a compound of formula (VIII).



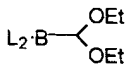
(VI)



(V)



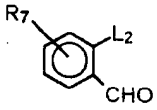
(VIII)



(VII)

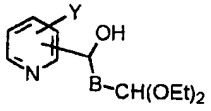
Compounds of formula (VIII), where R_7 is as previously assigned, can be obtained commercially or prepared from commercial compounds using the general process described by S. Nahm and S. Weinreb, Tetrahedron Lett., 1981, 22, 3815, using methods well known to a skilled person

In an alternative process compounds of formula (VI) can be prepared by the addition of the above mentioned reagents (VII) to an aldehyde of formula (IX) where L_2 and R_7 are as previously defined, followed by oxidation by the methods described below for the alcohol (X).

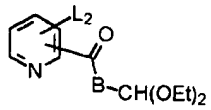


(IX)

Aldehydes of formula (IV) wherein A is pyridinoisoxazole can be prepared by oxidation of compounds of formula (X), in which two substituents on the pyridine ring have adjacent positions, to give compounds of formula (XII). The oxidation may typically be carried out using a suspension of chromium trioxide and dicalite in dichloromethane at room temperature or by using other methods well known in the art for the oxidation of alcohols to ketones such as chromium trioxide in pyridine or manganese dioxide in toluene at temperatures of 50-100 °C. Subsequent treatment of these ketones in the manner described above for ketones of formula (VI) gives the corresponding aldehydes of formula (IV) in which A is a pyridoisoxazole group.



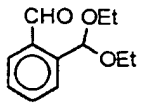
(X)



(XI)

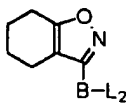
Compounds of formula (X) may be prepared by reaction of the appropriate lithio fluoro or chloropyridine derivatives, derived from the corresponding fluoro or chloro pyridine by treatment with a lithium amide base such as lithium diisopropylamide, with the aldehyde (XII). This latter aldehyde may be prepar d from o-bromobenzaldehyde diethyl acetal by treatment with n-

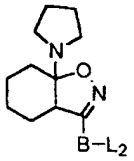
butyl lithium followed by reaction with dimethyl formamide using procedures well known in the art.



(XII)

Aldehydes of formula (IV) where A represents 4,5,6,7-tetrahydro-1,2-benzisoxazole may be prepared from a compound of formula (XIII) wherein L^2 is a halo atom for example bromo or chloro by treatment with an alkyl lithium reagent such as butyl lithium followed by dimethylformamide.



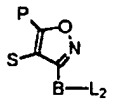


(XIII) (XIV)

Compounds of formula (XIII) may be prepared from compounds of formula (XIV) by the removal of elements of pyrrolidine in the presence of acid .

Compounds of formula (XIV) may be prepared by a 1,3-dipolar addition reaction as described in the literature M.E. Kuehne et. al. J. Org Chem. 1964, **29**, 1582.

Aldehydes of formula (IV) where A isoxazole or substituted isoxazole may be prepared from a compound of formula (XV) wherein L^2 is a halo atom for example bromo or chloro and P and S are as hitherto discribed by treatment with an alkyl lithium reagent such as butyl lithium followed by dimethylformamide.

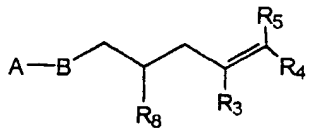


(XV) (XVI)

Compounds of formula (XV) where P and S are as hitherto discribed may be prepared from compounds of formula (XVI) where P and S are as hitherto discribed by a 1,3-dipolar addition reaction followed by an *in situ* dehydrohalogenation in a similar manner to that described in the literature M.E. Kuehne et. al. J. Org. Chem., 1964, **29**, 1582.

According to a third general process C, compounds of formula (I) wherein R_2 is an amino group and n=1 can be prepared by reacting a compound of

formula (XVa) wherein R_8 is an azido group with a suitable reducing agent, for example lithium aluminium hydride, sodium borohydride, or hydrazine in the presence of palladium or tin complexes. Alternatively, the reaction may be carried out with hydrogen and a suitable hydrogenation catalyst or with triphenylphosphine in a suitable mixture of solvents such as water and diethyl ether or tetrahydrofuran, for example at 20 °C to 60 °C.



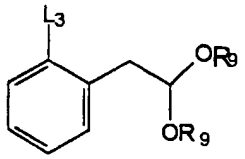
(XVa)

Compounds of formula (XVa) wherein R_8 is an azido group can be prepared from compounds of formula (XVa) wherein R_8 is a hydroxyl with a mixture of triphenylphosphine, diethyl azodicarboxylate and diphenylphosphoryl azide in an apolar solvent such as toluene or benzene at elevated temperature, for example 20 °C to 60 °C, or by reacting a compound of formula (XVa) wherein R_9 is a leaving group as hereinbefore described by substitution with inorganic azide salts in a polar solvent at an elevated temperature.

Compounds of formula (XVa) where R_8 is a hydroxyl group may be prepared by reaction of compounds of formula (XVII) with an appropriate organometallic reagent, such as a such as a Grignard, or a lithium or zinc reagent derived from $R_4R_5C{=}C(R_3)CH_2L^2$ in which L^2 is a suitable leaving group, such as a chloro or bromo atom, in the presence of an inert solvent such as hexane, toluene or tetrahydrofuran, at a temperature of -100°C to 100°C, typically at room temperature.

(XVII)

Compounds of formula (XVII) may be prepared by methods hereinbefore described utilizing aldehydes such as (XVIII) in which L_3 is a halogen such as chloro or bromo and R_{10} is a C_{1-6} alkyl or C_{3-5} cycloalkyl group, prepared by methods described in the literature (B. Wünsch, Arch. Pharm. (Weinheim) 1990, 323, 493).



(XVIII)

The present invention further includes all novel intermediates hereinbefore described.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

Example 1

The next section describes the methods used for

A) determining the potency of compounds to inhibit the hyperpolarisation-activated inward cation current I_h in dorsal root ganglion (DRG) cells of the rat; the effect is measured as the decrease in I_h activation rate and is expressed as the half maximal effect concentration (IC_{50}) or the negative logarithm of this IC_{50} (known as pIC_{50}).

B) determining the potency of compounds to inhibit marble burying behaviour in mice (BUR)

Methods

A) hyperpolarisation-activated cation current (I_h)

Culture of dissociated DRG neurons

To obtain E15 DRGs, pregnant Wistar rats were sacrificed. Embryos were removed and spinal cords with DRG attached to both sides were dissected out and collected in Hanks balanced salt solution (HBSS; Gibco). DRG were separated from the spinal cord and pooled in HBSS without Ca^{2+} and Mg^{2+}. Dissociation of intact DRG was started by incubation with a 0.25% trypsin solution for 30 min at 37°C. Trypsination was stopped by diluting the enzyme and centrifugation (1 min; 2500 rpm). After aspiration of the supernatant the tissue pellet was triturated with DMEMF10 (DMEM supplemented with 10% fetal bovine serum (Hyclone), 6 g/l glucose and 2 mM l-glutamine) and centrifuged for 10 min at 1700 rpm. Dissociated DRG cells were resuspended in culture medium (DMEMF10 with 50 ng/ml NGF 2.5S (Alomone labs)), counted and plated out in a density of 1 - $2 \cdot 10^5$ cells on collagen (50 µg/ml) and/or poly-l-lysine (10-20 µg/ml) coated glass coverslips in 24-well tissue culture plates. Plates were kept in a humidified incubator at 37°C and 5% CO_2 for 72 hrs. Glial cell proliferation was inhibited when necessary by adding cytosine arabinoside (Ara-c) at a concentration of 5.10^{-7} M. After 3 days fresh culture medium was administered. Medium was subsequently changed every 3-4 days.

Electrophysiological measurements

DRG cells were sampled with the whole cell voltage clamp method. Glass electrodes were pulled from thick-walled borosilicate capillaries with filament (1 mm outer diameter). Pipette resistance was 2-5 MΩ. Series resistance (5-15MΩ) was compensated for to ensure so that potential errors made in the determination of the actual membrane potential were less then 2 mV. Cell capacitance (10-75pF) compensation was used to compensate for capacitive currents. The extracellular solution contained (in mM): NaCl 140; KCl 5; $CaCl_2$ 2; $MgCl_2$ 1; D(+) glucose 5.6; HEPES 5; Sucrose 30; pH=7.4. The pipette solution contained (in mM): K-gluconate 119; NaCl 5; KCl 13; CsCl 2; $CaCl_2$ 1; EGTA 10; HEPES 10; pH=7.2. Cells were preincubated for more then 1½ hours with different concentrations (1E-9 to 1E-4 M) of test compound dissolved in extracellular solution at room temperature (20°C) in normal air. Larger cells that appeared round with a pronounced halo under phase-contrast microscopy were selected because almost all of them expressed I_h. Data were acquired with a Digidata 1200® analogue to digital interface using PCLAMP® software (both from Axon Instruments). For I_h activation the cell was held at -63 mV and stepped to -123mV (potentials after correction for liquid junction potential). Current traces were selected for soundness, averaged and fitted to a first order exponential using PCLAMP® software (fit between 60 and 950 ms to avoid biasing by transient currents). Activation time constants (τ) for I_h under different drug concentrations were derived from this fit. The activation rate constant for I_h is defined as $k_{act} = 1/\tau$.

Determination of (p)IC_{50} for inhibition of I_h

The pIC_{50} is the (-) log concentration of a compound at which the I_h activation rate constant k_{act} is reduced by 50%. pIC_{50} for a compound could be estimated adequately by fitting k_{act} to the logarithm of the concentration with a logistic function using PRISM® software (Graphpad Inc.). The function chosen is:

$k_{act} = A/(1+10^{(\log([compound])+pIC_{50})})$; A is k_{act} at [compound] = 0 M.

Averaging all control measurements yields that A = 3.52 s^{-1} and the maximum k_{act} was forced to this value for all compounds in this study. The Hill slope that normally is estimated in concentration-effect relations appeared to be

about 1 and was subsequently fixed to this value. The advantage of fixing Hill slope, minimum (k_{act} = 0 s^{-1}) and maximum (k_{act} = 3.52 s^{-1}) values is that only one parameter has to be estimated from a limited number of datapoints, which improves precision of the estimate.

B) marble burying behaviour in mice (BUR)

This assay was carried out essentially according to the procedure described by Treit et al. (1981) Pharmacol Biochem Behav; 15; 619-626

The results are presented as BUR log(ED_{50}) (s.c.). This is the logarithm of the effective dose (in µmol·kg^{-1}) causing 50% inhibition of burying compared to placebo-injected mice.

Results

A: The data presented in Table I demonstrate that there is a high correlation between the in vivo activity of a series of benzenemethaneamin derivatives, measured as inhibition of mice burying behaviour, and Ih inhibition.

Table I. *Summary of data for compound-induced inhibition of I_h activation rate constant (potency expressed as pIC_{50} (mean±SE)) and mice burying behaviour (potency expressed as log(ED_{50}); ED_{50} in µmol/kg).*

	PIC_{50}-I_h	SE	log(ED_{50}-BUR)
2-(1,2-benzisoxazol-3-yl)-α-methyl-benzenemethanamine hydrochloride	5.24	0.20	1.27
2-(6-chloro-1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine hydrochloride	6.44	0.18	0.32
(S)-(-)-2-(1,2-benzisoxazol-3-yl)-5-fluoro-α-2-propenyl-benzenemethanamine(E)-utenedioate	5.98	0.24	0.70
(S)-(-)-2-(6-fluoro-1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine(E)-butenedioate	6.13	0.14	0.40
(S)-(-)-2-(6-chloro-1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine hydrochloride	6.79	0.19	0.08
2-(1,2-benzisoxazol-3-yl)-*N*-benzyl-benzenemethanamine ethanedioate	5.06	0.12	1.65
(R)-2-(1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine hydrochloride	5.12	0.11	1.73
(S)-2-(1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine hydrochloride	6.48	0.17	0.11
2-(1,2-benzisoxazol-3-yl)-α-methyl-benzenemethanol	5.50	0.16	1.46
2-(1,2-benzisoxazol-3-yl)-α-butyl-benzenemethanamine hydrochloride	5.98	0.19	0.95

B: The in vivo activity of a number of methaneamine derivatives of the invention, measured as inhibition of mice burying behaviour, are shown in Table II and Table III. These compounds similarly demonstrate a correlation between Ih channel modulation and mice burying behaviour.

Table 2 *Mice burying behaviour (potency expressed in mg/kg)*

Example	*BUR sc ED50 (mg/kg)*
15 (4) = 2-phenyl-α-2-propenyl-benzenemethanamine hydrochloride	8.6
15 (6) = 2-(napth-1-yl)-α-2-propenyl-benzenemethanamine hydrochloride	11.6
15 (25) = 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-α-2-propenyl-benzene-methanamine (Z)-butenedioate	3.2
16 (2) = 2-(isoquinolin-4-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	9.9
16 (4) = 2-(thiazol-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	9
15 (14) = 2-(5-chlorothien-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	19
15 (34) = 2-(3-trifluoromethylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	6.9
15 (37) = 2-(4-chloro-2-fluorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	9
16 (7) = 2-(isoxazolo[4,5-c]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate	7.6
16 (6) = 2-(isoxazolo[5,4-c]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate	3.8

Table 3 Mice burying behaviour (potency expressed in mg/kg)

Compound	*BUR s.c. ED_{50} (mg/kg)*	*I_h amplitude*
Example 16(5) = 2-(isoxazolo[5,4-b]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate	1.7	90% inhibition at 1E-5 M

Example 2 : 2-(2-fluoro-4-methylphenyl)benzaldehyde.

A mixture of 2 g of 4-bromo-3-fluorotoluene, 1.75 g of 2-formylbenzeneboronic acid, 0.36 g of tetrakis(triphenylphosphine)-palladium (0) and 11.6 ml of 2N aqueous sodium carbonate, in 50 ml of a 9:1 mixture of toluene-ethanol was heated to 100 °C for 3 h. The mixture was cooled to room temperature, diluted with 100 ml of methylene chloride and washed with 50 ml of 5% sodium bicarbonate containing 5 ml of 0.88 M ammonia. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The resulting oil was purified by chromatography on silica gel eluting with ethyl acetate-heptane (1:3) to give 1.62 g of 2-(2-fluoro-4-methylphenyl)benzaldehyde as an oil, GC-M.S. (E.I.) (M/Z): 214 [M^+].

In a similar manner were prepared :

2-(benzo[b]thiophen-3-yl)benzaldehyde, starting from 3-bromobenzothiophene (prepared by the method of J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.* 1950, 72, 571), GC-M.S. (E.I.) (M/Z): 238 [M^+];

2-(napth-2-yl)benzaldehyde starting from 2-bromonapthalene, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.03 (CHO);

2-(benzo[b]furan-3-yl)benzaldehyde, starting from 3-bromobenzofuran (prepared by the method of D. S. Noyce and R. W. Nichols, *J. Org. Chem.* 1972, **37**, 4311), GC-M.S. (E.I.) (M/Z): 222 [M^+];

2-phenylbenzaldehyde starting from iodobenzene, GC-M.S. (E.I.) (M/Z): 182 [M^+];

2-(2-methoxyphenyl)benzaldehyde starting from 2-bromoanisole, GC-M.S. (E.I.) (M/Z): 212 [M^+];

2-(napth-1-yl)benzaldehyde starting from 1-bromonapthalene, GC-M.S. (E.I.) (M/Z): 232 [M^+];

2-(quinolin-3-yl)benzaldehyde starting from 3-bromoquinoline, melting at 83-85 °C;

2-(thien-3-yl)benzaldehyde starting from 3-bromothiophene, IR : 1694 cm^{-1};

2-(thien-2-yl)benzaldehyde starting from 2-bromothiophene, IR : 1691 cm^{-1};

2-(isoquinolin-4-yl)benzaldehyde starting from 4-bromoisoquinoline, GC-M.S. (E.I.) (M/Z): 233 [M^+];

2-(pyridin-3-yl)benzaldehyde starting from 3-bromopyridine, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.00 (CHO);

2-(4-pyrolinylphenyl)benzaldehyde starting from 1-(4-iodophenyl)pyrole, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.04 (CHO);
2-(thiazol-2-yl)benzaldehyde starting from 2-bromothiazole , melting at 76-77 °C;
2-(4-phenyl-3-fluorophenyl)benzaldehyde starting from 4-bromo-3-fluorobiphenyl, melting at 107-108 °C;
2-(furan-3-yl)benzaldehyde starting from 3-bromofuran, GC-M.S. (E.I.) (M/Z): 196 [M^+];
2-(3,5-dimethylisozazol-4-yl)benzaldehyde starting from 3,5-dimethyl-4-iodoisoxazole, melting at 128-129 °C;
2-benzylbenzaldehyde starting from benzyl bromide, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.25 (CHO);
2-(2-chlorophenyl)benzaldehyde starting from 2-bromochlorobenzene, GC-M.S. (E.I.) (M/Z): 215 [M^+-H];
2-(5-chlorothien-2-yl)benzaldehyde starting from 2-bromo-5-chlorothiophene, melting at 101-103 °C;
2-(3-fluoro-4-methylphenyl)benzaldehyde starting from 4-bromo-2-fluorotoluene, GC-M.S. (E.I.) (M/Z): 214 [M^+];
2-(3-fluoro-4-chlorophenyl)benzaldehyde starting from 4-bromo-2-chloro-1-fluorobenzene, GC-M.S. (E.I.) (M/Z): 234 [M^+];
2-(3-methoxybenzyl)benzaldehyde starting from 1-bromomethyl-3-methoxybenzene, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.25 (CHO);
2-(2-methoxybenzyl)benzaldehyde starting from 1-bromomethyl-2-methoxybenzene (prepared by the method of H. B. Misra and J. P. Shukla, *J. Indian Chem. Soc.* 1951, **28**, 277) , ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.35 (CHO);
2-(3-cyanophenyl)benzaldehyde starting from 3-bromobenzonitrile, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.95 (CHO);
2-(5-fluoro-2-methylphenyl)benzaldehyde starting from 2-bromo-4-fluorotoluene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.92 (CHO);
2-(4-methylphenyl)benzaldehyde starting from4-bromotoluene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 10.00 (CHO);
2-(3-trifluoromethylphenyl)benzaldehyde starting from 3-bromobenzotrifluoride, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.96 (CHO);
2-(4-fluorophenyl)benzaldehyde starting from 4-fluorobromobenzene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.98 (CHO);
2-(2-fluorophenyl)benzaldehyde starting from 1-bromo-2-fluorobenzene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.91 (CHO);

2-(4-chloro-2-fluorophenyl)benzaldehyde starting from1-bromo-4-chloro-2-fluorobenzene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.92 (CHO);
2-(5-chloro-2-methylphenyl)benzaldehyde staring from 2-bromo-4-chlorotoluene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.75 (CHO);
2-(3-chloro-2-methylphenyl)benzaldehyde staring from 2-bromo-5-chlorotoluene, ^{1}H-NMR (200 MHz, $CDCl_3$) d 9.72 (CHO);

Example 3 : 2-(benzoxazol-2-yl)benzaldehyde.

A mixture of 12.5 g of 2-tributylstannylbenzoxazole (prepared by the method of P. Jutzi and W. Gilge, *J. Organometallic Chem.* 1983, 246, 159, using tributyltin chloride as a less toxic replacement for trimethyltin chloride) 5.66 g 2-bromobenzaldehyde, and 0.46 g tetrakis(triphenylphosphine)-palladium (0) in 300 ml of anhydrous xylene under a nitrogen atmosphere was heated to 115 °C for 12 h. The reaction mixture was cooled to room temperature and evaporated to dryness under reduced pressure. The resulting oil was purified by chromatography on silica eluting with ethyl acetate-heptane (1:5) to afford 5.8 g of 2-(benzoxazol-2-yl)benzaldehyde, GC-M.S. (E.I.) (M/Z): 223 [M^+].

In a similar manner was prepared :
2-(benzothiazol-2-yl)benzaldehyde starting from 2-tributylstannylbenzothiazole (prepared by the method of P. Jutzi and W. Gilge, *J. Organometallic Chem.* 1983, **246**, 159, from benzothiazole, using tributyltin chloride as a less toxic replacement for trimethyltin chloride), melting at 117-120 °C.

Example 4 : 2-(benzo[b]furan-2-yl)benzaldehyde.

A mixture of 3 g of benzo[b]furan-2-boronic acid, 3.14 g 2-bromobenzaldehyde, 0.56 g tetrakis(triphenylphosphine)-palladium (0), and 17 ml of 2N aqueous sodium carbonate in 50 ml of a 9:1 mixture of toluene-ethanol, under a nitrogen atmosphere, was heated to 100 °C for 10 h. The mixture was cooled to room temperature, diluted with 100 ml of methylene chloride and washed with 50 ml of 5% sodium bicarbonate containing 5 ml of 0.88 M ammonia. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure to give 2-(benzo[b]furan-2-yl)benzaldehyde as a brown gum, GC-M.S. (E.I.) (M/Z): 222 [M^+].

In a similar manner were prepared :

2-(benzo[b]thiophen-2-yl)benzaldehyde starting from 2,4,6-tri(2-benzo[b]thienyl)cyclotriboroxane (prepared by the method of R. P. Dickinson and B. Iddon *J. Chem. Soc. (C)*, 1970, 1926), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.25 (CHO);

2-(5-fluorobenzo[b]thiophen-2-yl)benzaldehyde starting from 2,4,6-tri(2-(5-fluorobenzo[b]thienyl))cyclotriboroxane (prepared by the method of R. P. Dickinson and B. Iddon *J. Chem. Soc. (C)*, 1970, 1926), itself prepared from 5-fluorobenzo[b]thiophene (prepared by the method of B Février, G Dupas, J Bourguignon and G Quéguiner, *J. Heterocyclic Chem.*, 1983, **30**, 1085), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.24 (CHO);

2-(5-chlorobenzofuran-2-yl)benzaldehyde starting from 5-chlorobenzofuran-2-boronic acid (prepared by the method of R. P. Dickinson and B. Iddon *J. Chem. Soc. (C)* 1970, 1926), itself prepared from 5-chlorobenzo[b]furan (prepared by the method of T. Ota, S. Hasegawa, S Inoue and K. Sato, *J. Chem. Soc. Perkin Trans. I*, 1988, 3029) , ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.36 (CHO);

Example 5 : 2-(3a,4,5,6,7,7a-Hexahydro-7a-pyrrolidino-1,2-benzisoxazol-3-yl)-bromobenzene.

To a stirred solution of 6.3 g of 2-bromobenzohydroximinoyl chloride (A. Q. Hussein, M. M. El-Abadelah, W. S. Sabri, *J. Heterocycl. Chem.*, 1983, 20, 301) in 100 ml methylene chloride at room temperature was added 9.4 g of 1-pyrolidinocyclohexene (prepared by the method of M. E. Kuehne, *J. Am. Chem. Soc.*, 1959, 81, 5400) dropwise with external cooling. The solution was stirred for 19 h then evaporated and 150 ml of water was added and the suspension extracted with two 200 ml portions of methylene chloride. The combined organic layers were washed with 100 ml of brine and evaporated to an oil. To this oil was added 35 ml of methanol and the crystalline product filtered off to yield 5 g of 2-(3a,4,5,6,7,7a-hexahydro-7a-pyrrolidino-1,2-benzisoxazol-3-yl)-bromobenzene melting at 134 °C.

In a similar manner were prepared :

2-bromo-(5-phenylisoxazol-3-yl)benzene starting from a-bromostyrene; ^{1}H-NMR (400 MHz, $CDCl_3$) d 6.96 (C*H*CN);

2-bromo-(5-methylisoxazol-3-yl)benzene starting from 2-bromopropene; ^{1}H-NMR (400 MHz, $CDCl_3$) d 2.51 (Me);

2-bromo-(isoxazol-3-yl)benzene starting from vinylbromide; ^{1}H-NMR (400 MHz, $CDCl_3$) d 6.97 (C*H*CN);

Example 6 : 2-(4,5,6,7-Tetrahydro-1,2-benzisoxazol-3-yl)-bromobenzene.

To a stirred solution of 5.8 g of 2-(3a,4,5,6,7,7a-hexahydro-7a-pyrrolidino-1,2-benzisoxazol-3-yl)-bromobenzene in 60 ml of methanol was added 100 ml of concentrated hydrochloric acid and the solution was refluxed for 20 min. The solution was cooled to room temperature and neutralised with 10M potassium hydroxide solution. The solution was extracted with 400 ml then 200 ml of methylene chloride and the combined organic layers were dried over sodium sulfate and evaporated to yield 4.5 g of 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-bromobenzene as a gum, GC-M.S. (E.I.) (M/Z) : 277 $[M]^+$.

Example 7 : 2-(4,5,6,7-Tetrahydro-1,2-benzisoxazol-3-yl)-benzaldehyde.

To a solution of 4.1 g of 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-bromobenzene in 100 ml of ether at a temperature of -40 °C was added 11 ml of a 1.5M solution of butyllithium in hexane with magnetic stirring. The reaction was warmed to -20 °C and held at this temperature for 5 minutes. The lithio species was quenched by the addition of 1.3 ml of *N,N*-dimethylformamide. To the reaction was added 100 ml of saturated ammonium chloride and the solution was extracted with two 200 ml portions of ether. The combined organic layers were dried over sodium sulfate and evaporated to yield 3.5 g of 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-benzaldehyde, GC-M.S. (E.I.) (M/Z) : 226 $[M-H]^+$.

In a similar manner were prepared :
2-(5-phenylisoxazol-3-yl)benzaldehyde, starting from 2-bromo-(5-phenylisoxazol-3-yl)benzene melting at 90-97 °C;
2-(5-methylisoxazol-3-yl)benzaldehyde, starting from 2-bromo-(5-methylisoxazol-3-yl)benzene; ^{1}H-NMR (400 MHz, $CDCl_3$) d 2.54 (Me);
2-(isoxazol-3-yl)benzaldehyde, starting from 2-bromo-(isoxazol-3-yl)benzene; ^{1}H-NMR (400 MHz, $CDCl_3$) d 6.63 (C*H*CN);

Example 8 :2-formylbenzaldehyde diethylacetal

To a solution of 10.4 g of 2-bromobenzaldehyde diethyl acetal in 200 ml of dry diethyl ether at -65 °C was added 27.5 ml of a 1.6 M solution of butyllithium in hexanes. The solution was stirred at this temperature for 30 min. then slowly warmed to -40 °C when 3.4 ml of dimethylformamide was added dropwise. The reaction was warmed to room temperature then 100 ml of water was added and the organic layer was separated. The aqueous layer was extracted with two 100 ml portions of ether and the combined organic extracts were dried over sodium sulfate and evaporated to give 8.5 g of 2-formylbenzaldehyde diethylacetal as an oil; ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.06 (C*H*OEt).

Example 9 :(2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanol.

To a solution of 2.5 ml of diisopropylamine in 20 ml of dry tetrahydrofuran at -78 °C was added 11 ml of a 1.6 M solution of butyllithium in hexanes. The solution was stirred for 20 min. then a solution of 1.15 g of 2-fluoropyridine in 3 ml of tetrahydrofuran was added. The solution was stirred at -78 °C for 30 min then a solution of 2-formylbenzaldehyde diethylacetal in 3 ml of tetrahydrofuran was added dropwise. This solution was stirred for 1 h then warmed to room temperature overnight. The reaction was poured into a 5% solution of sodium carbonate and extracted with two 300 ml portions of ether. The combined organic layers were washed with 300 ml of water then the same volume of brine and dried over sodium sulfate. Evaporation of the solvent afforded (2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanol as a viscous oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.60 (C*H*OEt).

In a similar manner were prepared :
(3-fluoropyridin-4-yl)-2-(diethoxymethyl)-phenylmethanol starting from 3-fluoropyridine; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.58 (C*H*OEt);
(4-chloropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanol starting from 4-chloropyridine; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.63 (C*H*OEt);

Example 10 :(2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanone.

To a stirred suspension of 11.8 g of dicalite in 100 ml of dry methylene chloride was added 7.38 g of chromium trioxide. The suspension was stirred

for 30 min then a solution of (2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanol in 100 ml of methylene chloride was added. The supension was stirred overnight. The suspension was filtered through dicalite and washed with methylene chloride. The filtrate was washed with 100 ml portions of 1 M sodium hydroxide solution, water and brine and evaporated and azeotroped with toluene. Flash chromatography eluting with 30 to 50% ethyl acetate in heptane afforded (2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenyl-methanone as a gum; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.60 (C*H*OEt),

In a similar manner were prepared :
(3-fluoropyridin-4-yl)-2-(diethoxymethyl)-phenylmethane starting from (3-fluoropyridin-4-yl)-2-(diethoxymethyl)-phenylmethanol; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.75 (C*H*OEt);
(4-chloropyridin-3-yl)-2-(diethoxymethyl)-phenylmethane starting from (4-chloropyridin-3-yl)-2-(diethoxymethyl)-phenylmethanol; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.84 (C*H*OEt).

Example 11 : 2-(Isoxazolo[5,4-b]pyridin-3-yl)-benzaldehyde

To a solution of 0.49 g of acetone oxime in 8 ml of dry tetrahydrofuran was added 0.75 g of potassium *tert*-butoxide. The solution was stirred for 15 min. then a solution of 1.86 g of (2-fluoropyridin-3-yl)-2-(diethoxymethyl)-phenyl-methanone in 8 ml of tetrahydrofuran was added. The solution was stirred at room temperature for 30 min. then quenched by the addition of 25 ml of a 1:1 water-saturated ammonium chloride solution. The solution was extracted with two 50 ml portions of ether and the combined ether extracts were washed with brine and dried over sodium sulfate. Evaporation afforded the intermediate 3-[2-(diethyloxymethyl)-benzoyl]-2-[[(isopropylidene)amino]oxy]-pyridine which was not characterised but dissolved in 30 ml of ethanol and 20 ml of 2 M hydrochloric acid added and the solution refluxed for 15 min. The solution was cooled to room temperature and the crystals of 2-(isoxazolo[5,4-b]pyridin-3-yl)-benzaldehyde were collected by filtration and dried *in vacuo*, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.26 (CHO).

In a similar manner were prepared :
2-(Isoxazolo[5,4-c]pyridin-3-yl)-benzaldehyde starting from (3-chloropyridin-4-yl)-2-(diethoxymethyl)-phenylmethane; m.p 169-179 °C;

2-(Isoxazolo[4,5-c]pyridin-3-yl)-benzaldehyde starting from (4-chloropyridin-3-yl)-2-(diethoxymethyl)-phenylmethane; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 10.26 (CHO).

Example 12 : 3-Bromo-2-(diethoxymethyl)-benzo[b]furan

To a solution of 2.6 g of 3-bromo-2-benzo[b]furancarboxaldehyde (see M. Cugnon de Sevricourt and M. Robba, *Bull. Chim. Soc. Fr.*, 1977, 142) in 2.7 ml of triethyl orthoformate was added 33 mg of *para*-toluene sulfonic acid and the solution stirred at at roon temperature overnight. The solution was diluted with a 5% sodium carbonate solution and extracted with ether. The ether extracts were dried over sodium sulfate and evaporated to give 3-bromo-2-(diethoxymethyl)-benzo[b]furan as a liquid; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.76 (C*H*OEt).

In a similar manner was prepared :

3-Bromo-4-(diethoxymethyl)-thiophene, starting from 4-bromo-3-thiophenecarboxaldehyde (prepared by the method of D. W. Hawkins, B. Iddon, D. S. Longthorne and P. J. Rosyk, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.52 (C*H*OEt).

Example 13 : 2-(Diethoxymethyl)-3-(2-fluorobenzoyl)-benzo[b]furan

To a solution of 3 g of 3-bromo-2-(diethoxymethyl)-benzo[b]furan in 80 ml of dry ether under nitrogen at -100 °C was added 17.4 ml of a 1.7 M solution of *tert*-butyllithium in hexanes. The solution was stirred at the low temperature for 2 h then a solution of 2.76 g of *N*-methoxy-*N*-methyl-2-fluorobenzamide in 20 ml of dry ether was added and the solution stirred at the low tempertature for 10 min. The solution was then allowed to slowly warm to 0 °C, water was added and the organic layer was separated, washed with water and dried over sodium sulfate and evaporated. Gravity chromatography eluting 0 to 50% toluene in heptane afforded 0.91 g of 2-(diethoxymethyl)-3-(2-fluoro-benzoyl)-benzo[b]furan as an oil, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.76 (C*H*OEt).

In a similar manner were prepared :

2-(Diethoxymethyl)-5-(2-fluorobenzoyl)-thiophene, starting from 2-bromo-5-(diethoxymethyl)-thiophene (see D. J. Chadwick, J. Chambers, P. K. Hodgson, G. D, Meakins and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.75 (C*H*OEt);
2-(diethoxymethyl)-4-(2-fluorobenzoyl)-thiophene, starting from 3-bromo-5-(diethoxymethyl)-thiophene (see D. J. Chadwick, J. Chambers, P. K. Hodgson, G. D, Meakins and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.72 (C*H*OEt);
3-(diethoxymethyl)-4-(2-fluorobenzoyl)-thiophene, starting from 3-bromo-4-(diethoxymethyl)-thiophene, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.04 (C*H*OEt);
2-(diethoxymethyl)-3-(2-fluorobenzoyl)-thiophene, starting from 3-bromo-2-(diethoxymethyl)-thiophene (see D. J. Chadwick, J. Chambers, P. K. Hodgson, G. D, Meakins and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.13 (C*H*OEt);
2-(diethoxymethyl)-3-(2-fluorobenzoyl)-furan, starting from 3-bromo-2-(diethoxymethyl)-furan (see D. J. Chadwick, J. Chambers, P. K. Hodgson, G. D, Meakins and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2735), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.90 (C*H*OEt);

Example 14 : 3-(1,2-Benzisoxazol-3-yl)-2-benzo[b]furancarboxaldehyde

To a solution of 0.21 g of acetone oxime in 10 ml of dry tetrahydrofuran was added 0.32 g of potassium tert-butoxide and the suspension was stirred for 1 h. To this suspension was added a solution of 0.9 g of 2-(diethoxymethyl)-3-(2-fluorobenzoyl)-benzo[b]furan in 10 ml of tetrahydrofuran. The resulting solution was refluxed for 4.5 h then cooled to room temperature and brine added. The mixture was extracted with ether and the organic extracts were washed with water and dried over sodium sulfate. Evaporation afforded the crude 0.99 g of crude *O*-[2-[2-(diethoxymethyl)-3-benzo[b]furanoyl]phenyl]-oxime-2-propanone which was not characterised but dissolved in 10 ml of ethanol and 10 ml of 2 M hydrochloric acid added. The mixture was refluxed for 3 h the cooled to room temperature and and the precipitate collected and recrystallised from methylene chloride-ether to give 0.11 g of 3-(benzisoxazol-3-yl)-2-thiophenecarboxaldehyde melting at 173-174 °C.

In a similar manner were prepared :

5-(1,2-Benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, starting from 2-(diethoxymethyl)-5-(2-fluorobenzoyl)-thiophene, melting at 179-182 °C;
4-(1,2-benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, starting from 2-(diethoxymethyl)-4-(2-fluorobenzoyl)-thiophene, melting at 152-155 °C;
4-(1,2-benzisoxazol-3-yl)-3-thiophenecarboxaldehyde, starting from 3-(diethoxymethyl)-4-(2-fluorobenzoyl)-thiophene, melting at 150-153 °C;
3-(1,2-benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, starting from 2-(diethoxymethyl)-3-(2-fluorobenzoyl)-thiophene, melting at 154.5-155.5 °C;
3-(1,2-benzisoxazol-3-yl)-2-furancarboxaldehyde, starting from 2-(diethoxymethyl)-3-(2-fluorobenzoyl)-furan, melting at 191-192 °C.

Example 15 : 2-(benzo[b]furan-2-yl)-α-2-propenyl-benzenemethanamine hydrochloride.

To a solution of 3.0 g of 2-(benzo[b]furan-2-yl)-benzaldehyde in 60 ml of tetrahydrofuran, cooled at 0 °C under a nitrogen atmosphere, was added 16.2 ml of a 1 M solution of lithium bis(trimethylsilyl)amine in hexane. After stirring at 0 °C for 20 min 16.2 ml of a 1 M solution of allylmagnesium bromide in tetrahydrofuran was added and the resulting solution stirred at 0 °C for 40 min, then allowed to warm to room temperature over 1 h. Saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and evaporated to dryness under reduced pressure to give a brown oil. The compound was purified by chromatography on silica gel, eluting with 5% methanol in dichloromethane. The pure compound was dissolved in methanol and converted to its hydrochloride salt by addition of a solution of hydrogen chloride in methanol and crystallisation was initiated by addition of diethyl ether. The crystallised salt was filtered affording 2.4 g of 2-(benzo[b]furan-2-yl)-α-2-propenyl-benzenemethanamine hydrochloride, melting at 225-227 °C.

In a similar way were prepared :

(1) 2-(benzo[b]thiophen-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butene-dioate, starting from 2-(benzo[b]thiophen-3-yl)-benzaldehyde, melting at 185-187 °C;

(2) 2-(napth-2-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate, starting from 2-(napth-2-yl)benzaldehyde, melting at 182-185 °C;
(3) 2-(benzo[b]furan-3-yl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(benzo[b]furan-3-yl)benzaldehyde, melting at 160-165 °C;
(4) 2-phenyl-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-phenylbenzaldehyde, melting at 214-218 °C;
(5) 2-(2-methoxyphenyl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(2-methoxyphenyl)benzaldehyde, melting at 236-240 °C;
(6) 2-(napth-1-yl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(napth-1-yl)benzaldehyde, melting at 102-107 °C;
(7) 2-(thien-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(thien-3-yl)benzaldehyde, melting at 196-198 °C;
(8) 2-(thien-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(thien-2-yl)benzaldehyde, melting at 196-197 °C;
(9) 2-(4-pyrolinylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(4-pyrolinylphenyl)benzaldehyde, melting at 213-215 °C;
(10) 2-(4-phenyl-3-fluorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(4-phenyl-3-fluorophenyl)benzaldehyde, melting at 205-208 °C;
(11) 2-(furan-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(furan-3-yl)benzaldehyde, melting at 183-185 °C;
(12) 2-benzyl-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-benzylbenzaldehyde, melting at 181-183 °C;
(13) 2-(2-chlorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(2-chlorophenyl)benzaldehyde, melting at 189-191 °C;
(14) 2-(5-chlorothien-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(5-chlorothien-2-yl)benzaldehyde, melting at 192-199 °C;
(15) 2-(2-fluoro-4-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(2-fluoro-4-methylphenyl)benzaldehyde, melting at 209-211 °C;
(16) 2-(3-fluoro-4-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(3-fluoro-4-methylphenyl)benzaldehyde, melting at 194-196 °C;
(17) 2-(3-fluoro-4-chlorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(3-fluoro-4-chlorophenyl)benzaldehyde, melting at 192-194 °C;

(18) 2-(3-methoxybenzyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(3-methoxybenzyl)benzaldehyde, melting at 163-165 °C;

(19) 2-(2-methoxybenzyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(2-methoxybenzyl)benzaldehyde, melting at 172-174 °C;

(20) 2-(benzoxazol-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(benzoxazol-2-yl)benzaldehyde, melting at 202-204 °C;

(21) 2-(benzothiazol-2-yl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(benzothiazol-2-yl)benzaldehyde, melting at 240-242 °C;

(22) 2-(benzo[b]thiophen-2-yl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(benzo[b]thiophen-2-yl)benzaldehyde, melting at 106-108 °C;

(23) 2-(5-fluorobenzo[b]thiophen-2-yl)-α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(5-fluorobenzo[b]thiophen-2-yl)benzaldehyde, melting at 104-106 °C;

(24) 2-(5-chlorobenzofuran-2-yl) -α-2-propenyl-benzenemethanamine hydrochloride, starting from 2-(5-chlorobenzofuran-2-yl)benzaldehyde, melting at 226-228 °C;

(25) 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate starting from 2-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)-benzaldehyde, melting at 144-145 °C;

(26) 2-(1,2-benzisoxazol-3-yl)-α-2-propenyl-2-thiophenemethanamine (E)-butenedioate starting from 3-(benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, melting at 173-178 °C;

(27) 2-(1,2-benzisoxazol-3-yl)-α-2-propenyl-2-furanmethanamine (E)-butenedioate starting from 3-(1,2-benzisoxazol-3-yl)-2-furancarboxaldehyde, melting at 158-165 °C;

(28) 4-(1,2-benzisoxazol-3-yl)-α-2-propenyl-2-thiophenemethanamine (E)-butenedioate starting from 4-(1,2-benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, melting at 161-164 °C;

(29) 5-(1,2-benzisoxazol-3-yl)-α-2-propenyl-2-thiophenemethanamine (E)-butenedioate starting from 5-(1,2-benzisoxazol-3-yl)-2-thiophenecarboxaldehyde, melting at 182-189 °C;

(30) 4-(1,2-benzisoxazol-3-yl)-α-2-propenyl-3-thiophenemethanamine (E)-butenedioate (2:1 salt) starting from 4-(1,2-benzisoxazol-3-yl)-3-thiophenecarboxaldehyde, melting at 188-190 °C;

(31) 3-(1,2-benzisoxazol-3-yl)-α-2-propenyl-2-benzo[b]furanmethanamine (E)-butenedioate starting from 3-(1,2-benzisoxazol-3-yl)-2-benzo[b]furancarboxaldehyde, melting at 210-216 °C;

(32) 2-(5-fluoro-2-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(5-fluoro-2-methylphenyl)benzaldehyde, melting at 190-192°C;
(33) 2-(4-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(4-methylphenyl)benzaldehyde, melting at 198-200°C;
(34) 2-(3-trifluoromethylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(3-trifluoromethylphenyl)benzaldehyde, melting at 194-196°C;
(35) 2-(4-fluorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(4-fluorophenyl)benzaldehyde, melting at 201-203°C;
(36) 2-(2-fluorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(2-fluorophenyl)benzaldehyde melting at 225-226°C;
(37) 2-(4-chloro-2-fluorophenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(4-chloro-2-fluorophenyl)benzaldehyde, melting at 213-215°C;
(38) 2-(5-chloro-2-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(5-chloro-2-methylphenyl)benzaldehyde, melting at 179-184°C;

(39) 2-(3-chloro-2-methylphenyl)-α-2-propenyl-benzenemethanamine (E)-butenedioate staring from 2-(3-chloro-2-methylphenyl)benzaldehyde, melting at 192-196°C;
(40) 2-(5-phenylisoxazol-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(5-phenylisoxazol-3-yl)benzaldehyde, melting at 165-180 °C;
(41) 2-(5-methylisoxazol-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate, starting from 2-(5-methylisoxazol-3-yl)benzaldehyde, melting at 130-138 °C.

Example 16 : 2-(3,5-dimethylisozazol-4-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate.

To a stirred suspension of 1 g of 2-(3,5-dimethylisozazol-4-yl)benzaldehyde and 2.4 g of anhydrous magnesium sulfate was added 0.86 ml of diphenylmethanamine, and the stirring continued overnight. The reaction was filtered through dicalite and the filtrate evaporated to give an oil that crystallised on addition of diethyl ether and cooling to 4 °C, to give 1.55 g of *N*-[2-(3,5-dimethylisoxazol-4-yl)-benzylidene]-1,1-diphenylmethanamine, melting at 165-167 °C. A stirred solution of 0.81 g of *N*-[2-(3,5-dimethyl-

isoxazol-4-yl)-benzylidene]-1,1-diphenylmethanamine in 15 ml of tetrahydrofuran was cooled to -78 °C and 6.6 ml of a 1 M solution of potassium tert-butoxide in tetrahydrofuran was added dropwise. The purple coloured solution was stirred for 15 min then 0.57 ml of allyl bromide was added rapidly and the reaction allowed to slowly warm to room temperature. The reaction mixture was diluted with 25 ml of saturated aqueous ammonium chloride and extracted into dichloromethane. The combined organic extracts were dried over sodium sulfate then evaporated to give crude *N*-(diphenylmethylidene)-2-(3,5-dimethylisozazol-4-yl)-α-2-propenyl-benzene-methanamine which was not characterised due to instability. The crude product was dissolved in 15 ml of acetone and 5 ml of 1M hydrochloric acid added. The solution was stirred overnight and then the acetone was removed by evaporation and the crude product was redissolved in 20 ml of dichloromethane. The solution was extracted with two 20 ml portions of 2N hydrochloric acid. The combined acid extracts were washed with 10 ml of dichloromethane and then basified with 4N sodium hydroxide solution. The basic extracts were combined and re-extracted with three 20 ml portions of dichloromethane, the combined organic extracts were dried over sodium sulfate and evaporated to give 153 mg of product. The product was dissolved in 1 ml of methanol and 73 mg of fumaric acid was added. The product was crystallised by trituration with ether and cooling to 4 °C to yield 167 mg of 2-(3,5-dimethylisozazol-4-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, melting at 198-200 °C.

In a similar manner were prepared :

(1) 2-(quinolin-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(quinolin-3-yl)-benzaldehyde, melting at 194-197 °C;
(2) 2-(isoquinolin-4-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(isoquinolin-4-yl)-benzaldehyde, melting at 246-248 °C;
(3) 2-(pyrimidin-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(pyrimidin-3-yl)benzaldehyde, melting at 75-77 °C;
(4) 2-(thiazol-2-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(thiazol-2-yl)benzaldehyde, melting at 156-161 °C;
(5) 2-(isoxazolo[5,4-b]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate starting from 2-(isoxazolo[5,4-b]pyridin-3-yl)-benzaldehyde, melting at 187-188 °C (dec);

(6) 2-(isoxazolo[5,4-c]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate starting from 2-(isoxazolo[5,4-c]pyridin-3-yl)-benzaldehyde, melting at 183-189 °C;

(7) 2-(isoxazolo[4,5-c]pyridin-3-yl)-α-2-propenyl-benzenemethanamine (Z)-butenedioate starting from 2-(isoxazolo[4,5-c]pyridin-3-yl)-benzaldehyde, melting at 151-153 °C;

(8) 2-(isoxazol-3-yl)-α-2-propenyl-benzenemethanamine (E)-butenedioate, starting from 2-(isoxazol-3-yl)benzaldehyde, melting at 150-175 °C.

Example 17 : 2-(3-cyanophenyl)-α-2-propynyl-benzenemethanamine

To a stirred suspension of 3.58 g of 2-(3-cyanobenzyl)benzaldehyde and 10.4 g of anhydrous magnesium sulfate was added 3.6 ml of diphenylmethanamine, and the stirring continued overnight. The reaction was filtered through dicalite and the filtrate evaporated to give an oil that crystallised on addition of diethyl ether and cooling to 4 °C, to give 4.11 g of *N*-[2-(3-cyanobenzyl)benzylidene]-1,1-diphenylmethanamine, melting at 113-115 °C. A stirred solution of 1.0 g of *N*-[2-(3-cyanobenzyl)benzylidene]-1,1-diphenylmethanamine in 15 ml of tetrahydrofuran was cooled to -78 °C and 6.7 ml of a 1 M solution of potassium tert-butoxide in tetrahydrofuran was added dropwise. The purple coloured solution was stirred for 20 min then 0.9 ml of propargyl bromide was added rapidly and the reaction allowed to slowly warm to room temperature. The reaction mixture was diluted with 25 ml of saturated aqueous ammonium chloride and extracted into dichloromethane. The combined organic extracts were dried over sodium sulfate the evaporated to give crude *N*- (diphenylmethylidene)-2-(3-cyanobenzyl)-α-2-propynyl-benzenemethanamine which was not characterised due to instability. The crude product was dissolved in 20 ml of acetone and 5 ml of 1M hydrochloric acid added. The solution was stirred at room temperature for 3 h then cooled to 4 °C overnight. The acetone was removed by evaporation and the crude product redissolved in 20 ml of dichloromethane. The solution was extracted with two 20 ml portions of 2N hydrochloric acid. The combined acid extracts were washed with 10 ml of dichloromethane and then basified with 4N sodium hydroxide solution. The basic extracts were combined and re-extracted with three 20 ml portions of dichloromethane, the combined organic extracts were dried over sodium sulfate and evaporated to give 120 mg of product. The product was dissolved in 1 ml of methanol and 57 mg of fumaric acid was added. The product was crystallised by trituation with ether and cooling to 4

°C to yield 120 mg of 2-(3-cyanobenzyl)-α-2-propynyl-benzenemethanamine (E)-butenedioate, melting at 182-184 °C.

In a similar manner was prepared :

2-(isoxazolo[5,4-b]pyridin-3-yl)-α-2-propynyl-benzenemethanamine (Z)-butenedioate starting from 2-(isoxazolo[5,4-b]pyridin-3-yl)-benzaldehyde, melting at 180-185 °C (dec).

Example 18 : [2-(2-Dimethoxyethyl)-phenyl](2-fluorophenyl)-methanone

A stirred solution of 10.0 g of 2-(2-bromophenyl)acetaldehyde dimethylacetal (B. Wünsch, *Arch. Pharm. (Weinheim)* 1990, **323**, 493) in 100 ml of anhydrous tetrahydrofuran was cooled to -78 °C under a nitrogen atmosphere. To this solution was added 29.3 ml of a 1.6 M solution of n-butyllithium in hexane. The solution was warmed to 30 °C over 30 min during which time a precipitate formed. The suspension was re-cooled to -78 °C and a solution of 7.46 g of *N*-methoxy-*N*-methyl-2-fluorobenzamide in 100 ml of tetrahydrofuran was added by cannular. The solution was warmed to room temperature and stirred for 1 h, then quenched by the addition of 100 ml of water and extracted with 300 ml then 200 ml of dichloromethane. The combined organic extracts were dried over sodium sulfate and evaporated to yield crude product which was purified by chromatography on silica gel, eluting with 15 % ethyl acetate in hexane, affording 6.81 g of [2-(2-dimethoxy-ethyl)-phenyl](2-fluorophenyl)-methanone, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.29 (CH_3).

Example 19 : 2-[2-(1,2-benzisoxazol-3-yl)-phenyl] acetaldehyde

To a solution of 1.91g of acetone oxime in 40 ml of tetrahydrofuran was added 2.93 g of potassium *tert*-butoxide. The suspension was stirred for 30 min then a solution of 6.81 g of [2-(2-dimethoxyethyl)-phenyl](2-fluoro-phenyl)-methanone in 30 ml of tetrahydrofuran was added and the solution was heated to reflux for 12 h. The solution was cooled to room temperature and diluted with 100 ml of water then extracted with 200 ml then 100 ml of ethyl acetate. The combined organic extracts were washed with 100 ml of brine then dried over sodium sulfate and evaporated to give 7.91 g of crude *O*-[2-(2-dimethoxyethyl)benzoyl-2-phenyl]-oxime 2-propanone. This material was dissolved in 90 ml of ethanol and 90 ml of 2N hydrochloric acid was

added. The resulting mixture was heated to reflux for 3 h. After cooling to room temperature most of the organic solvent was removed by evaporation and the residual aqueous solution was extracted with 200 ml then 100 ml of dichloromethane. The combined organic extracts were washed with 100 ml of brine then dried over sodium sulfate, and evaporated to give 6.9 g of a mixture of the desired product and its corresponding diethyl acetal. This material was redissolved in 30 ml of chloroform and cooled to 0 °C. To this solution was added 10 ml of a 50% aqueous solution of trifluoroacetic acid and the resulting mixture stirred at 0 °C for 3 h then at room temperature for 12 h. The reaction was quenched by adding 100 ml of water and the aqueous solution was extracted with 200 ml then 100 ml of dichloromethane. The combined organic extracts were washed with 100 ml of 5 % sodium carbonate solution then dried over sodium sulfate and evaporated to give 5.5 g of crude 2-[2-(1,2-benzisoxazol-3-yl)-phenyl] acetaldehyde, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.75 (CHO).

Example 20 : 3-[2-(2-Hydroxy-4-pentenyl)phenyl]-1,2-benzisoxazole

To a stirred solution of 2 g of 2-[2-(1,2-benzisoxazol-3-yl)-phenyl] acetaldehyde in 50 ml of tetrahydrofuran at -78 °C under a nitrogen atmosphere was added 10 ml of a 1 M solution of allyl magnesium bromide in diethyl ether. The solution was warmed to room temperature and stirred for a further 2 h then quenched by addition of 50 ml of saturated aqueous ammonium chloride. The aqueous layer was extracted with 150 ml then 100 ml of dichloromethane and the combined organic extracts dried over sodium sulfate and evaporated to give crude product which was purified by chromatography eluting with 20% ethyl acetate in hexane, affording 1 g of 3-[2-(2-Hydroxy-4-pentenyl)phenyl]-1,2-benzisoxazole, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.8 (CH=CH_2).

Example 21 : 3-[2-(2-Azido-4-pentenyl)phenyl]-1,2-benzisoxazole

To a stirred solution of 1.0 g of 3-[2-(2-Hydroxy-4-pentyl)phenyl]-1,2-benzisoxazole and 1.0 g of triphenylphosphine in 20 ml of tetrahydrofuran at 0 °C was added 0.56 ml of diethyl azodicarboxylate followed by dropwise addition of 1.36 ml of diphenylphosphoryl azide. The solution was stirred at 0 °C for 1 h then warmed to room temperature and stirred a furth r 2 h. The reaction was quenched with 50 ml of water and extracted with 100 ml then 50 ml of dichloromethane. The combined organic fractions were dried over sodium

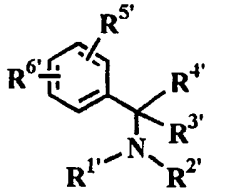
sulfate and evaporated to give crude product, which was purified by chromatography on silica gel eluting with 7 % ethyl acetate in hexane, affording 0.65 g of 3-[2-(2-azido-4-pentenyl)phenyl]-1,2-benzisoxazole, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.68 (C*H*=CH_2).

Example 22 : 3-[2-(2-amino-4-pentenyl)phenyl]-1,2-benzisoxazole (E)-butenedioate

To a stirred solution of 631 mg of 3-[2-(2-azido-4-pentenyl)phenyl]-1,2-benzisoxazole in 10 ml of anhydrous tetrahydrofuran at -40 °C under a nitrogen atmosphere was added 2.07 ml of a 1 M solution of lithium aluminium hydride in diethyl ether. The reaction mixture was warmed to room temperature then heated to 60 °C for 1 h. After cooling to room temperature and careful quenching with 4 N sodium hydroxide, 50 ml of water was added and the product extracted with 100 ml then 50 ml of dichloromethane. The combined organic extracts were dried over sodium sulfate and the solvent removed by evaporation to give crude product which was purified by chromatography on silica gel eluting with 10% methanol in dichloromethane, to give 315 mg of 3-[2-(2-amino-4-pentenyl)phenyl]-1,2-benzisoxazole. The product was dissolved in 1 ml of methanol and 131 mg of fumaric acid was added. Addition of diethyl ether and cooling to 4 °C led to crystallisation of 313 mg of 3-[2-(2-amino-4-pentenyl)phenyl]-1,2-benzisoxazole (E)-butenedioate, melting at 170-172 °C.

CLAIMS

1. Use of an I_h channel modulator in the manufacture of a medicament for use in the treatment or prevention of a psychiatric disorder, with the proviso that the modulator is not a compound of formula (D)


(D)

wherein

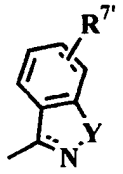
$R^{1'}$ and $R^{2'}$, which may be the same or different, are each selected from C_{6-12}aryl, C_{2-14}heteroaryl, C_{6-12}arylC_{1-6}alkyl, C_{2-14}heteroarylC_{1-6}alkyl (where the alkyl, aryl or heteroaryl moiety may be optionally substituted by one or more substituents selected from C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{4-6}cycloalkenyl, C_{6-12}aryl, C_{2-14}heteroaryl, halogen, amino, hydroxy, haloC_{1-6}alkyl, nitro, C_{1-6}alkylthio, sulphonamide, C_{1-6}alkylsulphonyl, hydroxy-C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, carboxyl, carboxyC_{1-6}alkyl, carboxamide and C_{1-6}alkylcarboxamide), hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{4-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxyC_{1-6}alkyl (where the alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, or alkoxyalkyl moieties may be optionally substituted by one or more substituents selected from amino, halogen, hydroxy, C_{1-6}alkylcarboxamide, carboxamide, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarboxy and carboxyC_{1-6}alkyl) or one of $R^{1'}$ and $R^{2'}$ are as hereinbefore defined and one is hydroxy;

$R^{3'}$ and $R^{4'}$, which may be the same or different, are each selected from C_{6-12}aryl, C_{2-14}heteroaryl, C_{6-12}arylC_{1-6}alkyl, C_{2-14}heteroarylC_{1-6}alkyl (where the alkyl, aryl or heteroaryl moiety may be optionally substituted by one or more substituents selected from C_{1-6}alkoxy, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{4-6}cycloalkenyl, C_{6-12}aryl, C_{2-14}heteroaryl, halogen, amino, hydroxy, halo-C_{1-6}alkyl, nitro, C_{1-6}alkylthio, sulphonamide, C_{1-6}alkylsulphonyl, hydroxy C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, carboxyl, carboxyC_{1-6}alkyl, C_{1-6}alkylcarboxamide and carboxamide), hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{4-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{2-6}alkenyl, haloC_{2-6}alkynyl, cyano, carboxyl, C_{1-6}alkylcarboxy and carboxyC_{1-6}alkyl (where the alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, or alkoxyalkyl moieties may be optionally substituted by one or more substituents selected from amino, hydroxy, C_{1-6}alkylcarboxamide, carboxamide, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarboxy and carboxy-

C_{1-6}alkyl); or one of $R^{3'}$ or $R^{4'}$ together with one of $R^{1'}$ or $R^{2'}$ and the N atom to which it is attached form a 5- or 6-membered heterocyclic ring.

$R^{5'}$ represents one or more ring substituents selected from halogen, hydrogen C_{1-6}alkyl and C_{1-6}alkoxy; and

$R^{6'}$ represents a single ring substituent of formula:



wherein the dotted line represents an optional bond; Y is oxygen or $-NR^{8'}$ (where $R^{8'}$ is hydrogen or C_{1-6}alkyl) and $R^{7'}$ represents one or more substituents selected from hydrogen, halogen, haloC_{1-6}alkyl, C_{1-6}alkyl and C_{1-6}alkoxy.

2. Use according to claim 1 wherein the psychiatric disorder is depression, anxiety or psychosis.

3. Use according to claim 1 or 2, wherein the I_h channel modulator has a pIC_{50} of more than 5 in an I_h channel modulator functional assay.

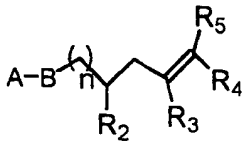
4. Use according to claim 3, wherein the pIC_{50} is in the range of 6 to 9.

5. Use of an I_h channel modulation assay for identifying compounds useful for the treatment or prevention of psychiatric disorders.

6. Use of an assay according to claim 5 comprising:

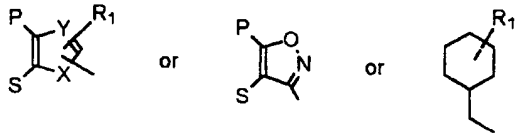
- taking a brain slice, or a cultured brain slice, or ganglia of the peripheral nervous system, or primary cell cultures of central and/or peripheral nervous tissue, or cell lines expressing Ih channels
- incubating and/or exposing these cells and tissues to test compounds and
- measuring whether these test compounds affect conductance of the I_h channel and/or the open probability.

7. A compound of formula (I)



(I)

wherein A is a group selected from (a), (b) or (c):-



(a) (b) (c)

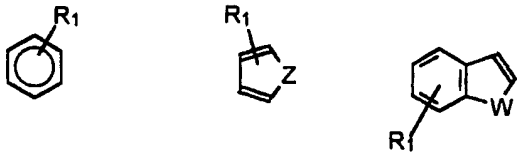
wherein Y is CH or N;

X is O, S, CH=CH, or CH=N;

P and S, which may be the same or different, each represent hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl or pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; or P and S together with the ethylene group to which they are bonded form a 1,2-phenylene, a pyridinediyl (including 2,3- and 3,4-pyridinediyl), or a 1-cyclohexen-1,2-diyl group, which groups may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl;

R_1 represents one or more ring substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl;

B is a bivalent carbon radical derived from an aromatic group selected from (d), (e) or (f):



(d) (e) (f)

wherein Z is O or S; W is O, S or CH=CH; R_1 is as hereinbefore defined;

R_2 is NH_2

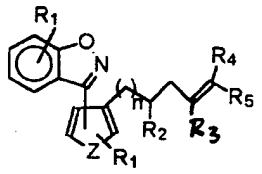
R_3, R_4, and R_5, which may be the same or different, each represent halogen, C_{1-4}alkyl or hydrogen, or R_3 and R_4 together form a carbon-carbon bond;

n is 0 or 1;

or a physiologically acceptable salt or solvate thereof;

with the proviso that when A is group (b) wherein P and S together with the ethylene group to which they are bonded form a 1,2-phenylene group, which group may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl, phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; R_2, R_3, R_4 and R_5 are as herein before defined and n is 0; then B is a group (e) or (f).

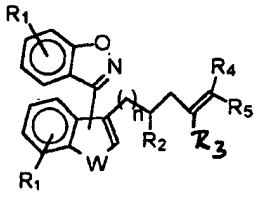
8. A compound according to claim 7 of formula (IA)



(IA)

wherein Z, R_1, R_2, R_3, R_4 and R_5 are as defined in claim 7 and n is 0; or a physiologically acceptable salt or solvate thereof.

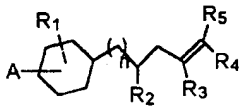
9. A compound according to claim 7 of formula (IB)



(IB)

wherein W, R_1, R_2, R_3, R_4 and R_5 are as defined in claim 7 and n is 0; or a physiologically acceptable salt or solvate thereof.

10. A compound according to claim 7 of formula (IC)



(IC)

wherein A, R_1, R_2, R_3, R_4 and R_5 are as defined in claim 7 and n is 0 or 1, preferably n is 0; or a physiologically acceptable salt or solvate thereof;

with the proviso that A is not a group (b) wherein P and S together with the ethylene group to which they are bonded form a 1,2-phenylene group, which group may be optionally substituted by one or more substituents selected from hydrogen, C_{1-4}alkyl, C_{1-3}alkoxy, cyano, halogen, trifluoromethyl phenyl and pyrrole wherein the phenyl or pyrrole moieties may be optionally substituted with halogen or C_{1-3}alkyl; R_2, R_3, R_4 and R_5 are as defined in claim 1 and n is 0; or a physiologically acceptable salt or solvate thereof.

11. A compound of formula (I) or a physiologically acceptable salt or solvate thereof, as defined according to any of claims 7 to 10 for use in therapy.

12. Use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof, as defined according to any of claims 7 to 10 in the manufacture of a medicament for the treatment or prevention of a psychiatric disorder.

13. A pharmaceutical formulation containing a compound of formula (I) or a physiologically acceptable salt or solvate thereof, as defined according to any of claims 7 to 10, together with a pharmaceutically acceptable carrier therefor.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 31/00, 31/135, 31/42, 31/425, 31/435,
(Continued on the following page)

A3

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Published
With international search report.

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13 January 2000 (13.01.00)

(54) Title: I_h–MODULATORS

(57) Abstract

The present invention relates to the use of an I_h channel modulator in the manufacture of a medicament for use in psychiatry. To certain novel methanamine derivatives, to processes for their preparation, to pharmaceutical formulations containing them and to their use in medical therapy, particularly for use in psychiatry.

31/47, 31/34, 31/38, G01N 33/50, C07D 307/81, 333/58, 333/20, 307/52, 333/28, 263/56, 277/66, 261/20, 413/04, 261/08, 215/12, 217/14, 239/26, 277/28, 498/04, C07C 211/29, 211/28

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06651

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/135 A61K31/42 A61K31/425 A61K31/435
A61K31/47 A61K31/34 A61K31/38 G01N33/50 C07D307/81
C07D333/58 C07D333/20 C07D307/52 C07D333/28 C07D263/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N.C. HARRIS ET AL.: "Mechanism of Block by ZD 7288 of the Hyoerpolarization-Activated Inward Rectifying Current in Guinea Pig Substantia Nigra Neurons In Vitro" J. NEUROPHYSIOL., vol. 74, no. 6, 1995, pages 2366-2378, XP002108866 cited in the application see abstract see page 2377, left-hand column --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1999	10. 11. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	THEUNS, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06651

A. CLASSIFICATI N OF SUBJECT MATTER
IPC 6 C07D277/66 C07D261/20 C07D413/04 C07D261/08 C07D215/12
C07D217/14 C07D239/26 C07D277/28 C07D498/04 C07C211/29
C07C211/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C. OGURA ET AL.: "Clinical effect of L-dopa on schizophrenia" DIALOG (R) FILE 155: MEDLINE (R), ACCESSION NUMBER 03083769: CURR. THER. RES. CLIN. EXP., vol. 20, no. 3, September 1976, pages 308-318, XP002108867 see abstract ---	1-4
X	A. SOBOLL-TERRAUX: "EFFET DE LA L-DOPA SUR LE COMPORTEMENT PSYCHOMOTEUR. PERSPECTIVES THERAPEUTIQUES EN PSYCHIATRIE." DIALOG (R) FILE 144: PASCAL (R), ACCESSION NUMBER 01896639: THESIS, 1976, pages 1-99, XP002108868 see abstract --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1999	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	THEUNS, H

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INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 98/06651

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.R.SMYTIES: "The neurochemical basis of psychiatry" DIALOG (R) FILE 155: MEDLINE (R), ACCESSION NUMBER 04436109: ALA. J. MED.SCI., vol. 17, no. 2, April 1980, pages 159-161, XP002108869 see abstract	1-4
X	EP 0 130 303 A (SOCIETE DES PRODUITS NESTLE S.A.) 9 January 1985 see page 1, line 6 - line 19	1-4
X	M.H. SHEARD: "The effect of lithium and other ions on aggressive behavior" DIALOG (R) FILE 155: MEDLINE (R), ACCESSION NUMBER 02882892: MOD. PROBL. PHARMACOPSYCHIATRY, vol. 13, 1978, pages 53-68, XP002108870 see abstract line 19	1-4
X	P. CHOTEAU ET AL.: "LITHIUM ET ABORD THERAPEUTIQUE DE LA MALADIE CYCLIQUE" DIALOG (R) FILE: 144 PASCAL (C), ACCESSION NUMBER 04213923: J. SCI. MED. LILLE, vol. 92, no. 11, 1974, pages 345-352, XP002108871 see abstract line 19	1-4
A	N.C.HARRIS ET AL.: "Selective blockade of the hyperpolarization-activated cationic current (Ih) in guinea pig substantia nigra pars compacta neurones by a novel bradycardic agent, Zeneca ZM 227189" NEUROSCI. LETT., vol. 176, 1994, pages 221-225, XP002108872 cited in the application see abstract line 19	1-4
A	H.C.PAPE: "SPECIFIC BRADYCARDIC AGENTS BLOCK THE HYPERPOLARIZATION-ACTIVATED CATION CURRENT IN CENTRAL NEURONS" NEUROSCIENCE, vol. 59, no. 2, 1994, pages 363-373, XP002108873 cited in the application see page 371, right-hand column - line 19	1-4

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2

INTERNATIONAL SEARCH REPORT

Inte. ..tional Application No
PCT/EP 98/06651

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	H.C.PAPE: "QUEER CURRENT AND PACEMAKER: The Hyperpolarization-Activated Cation Current in Neurons" ANNU. REV. PHYSIOL., vol. 58, 1996, pages 299-327, XP002108874 cited in the application see abstract line 19 ---	1-4
X,P	WO 97 40027 A (AKZO NOBEL N.V.) 30 October 1997 cited in the application see the whole document line 19 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/06651

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:
See additional sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-4
2. Claims: 5-6
3. Claims: 7, 11-13 (all partially)
4. Claims: 7, 11-13 (all partially)
5. Claims: 8,9 and partially 7,11-13
6. Claims: 7, 11-13 (all partially)
7. Claims: 10, and partially 7, 11-13

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-4

Use of an Ih channel modulator in the manufacture of a medicament for use in the treatment or prevention of a psychiatric disorder, excluding the subject matters of inventions 2-7.

2. Claims: 5-6

Use of an Ih channel modulation assay for identifying compounds useful for the treatment or prevention of psychiatric disorders, excluding the subject matters of inventions 1, and 3-7.

3. Claims: 7, 11-13 (all partially)

Compounds of formula (I) having A equal to (a) having X equal to O or S, excluding the subject matters of inventions 1-2, and 4-7.

4. Claims: 7, 11-13 (all partially)

Compounds of formula (I) having A equal to (a) having X equal to CH=CH or CH=N, excluding the subject matters of inventions 1-3, and 5-7.

5. Claims: 8,9 and partially 7, 11-13

Compounds of formula (I) having A equal to (b), excluding the subject matters of inventions 1-4, and 6-7.

6. Claims: 7, 11-13 (all partially)

Compounds of formula (I) having A equal to (c), excluding the subject matters of inventions 1-5, and 7.

7. Claims: 10, and partially 7, 11-13

Compounds of formula (IC), excluding the subject matters of inventions 1-6.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 2

Continuation of Box 3.

Claims Nos.: 1-4 (partially)

Present claims 1-6 relate to the use or identification of a compound defined (inter alia) by reference to the following parameter(s):
P1: Ih channel modulation;
P2: pIC50 in an (otherwise undefined) Ih channel modulator functional assay;
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the general concept underlying the presently searched claims 1-4.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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Intr ·tional Application No
PCT/EP 98/06651

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